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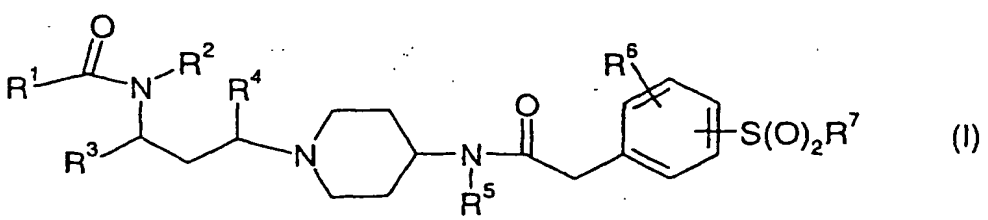
(54) Title: NOVEL PIPERIDINE DERIVATIVES AS MODULATORS OF CHEMOKINE RECEPTORS



(I)

(57) Abstract: Compounds of the invention, for example compounds of formula (I): compositions comprising them, processes for preparing them and their use in medical therapy (for example modulating CCR5 receptor activity in a warm blooded animal).

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Novel piperidine derivatives as modulators of chemokine receptors.

The present invention relates to heterocyclic derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in PCT/SE01/01053, EP-A1-1013276, WO00/08013, WO99/38514 and WO99/04794.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

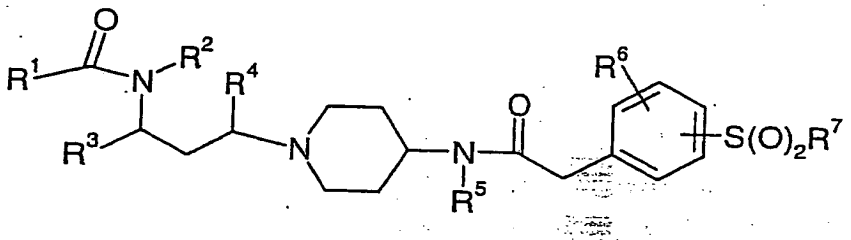
The CCR5 receptor is expressed on T-lymphocytes, monocytes, macrophages, dendritic cells, microglia and other cell types. These detect and respond to several

chemokines, principally "regulated on activation normal T-cell expressed and secreted" (RANTES), macrophage inflammatory proteins (MIP) MIP-1α and MIP-1β and monocyte chemoattractant protein-2 (MCP-2).

This results in the recruitment of cells of the immune system to sites of disease. In many diseases it is the cells expressing CCR5 which contribute, directly or indirectly, to tissue damage. Consequently, inhibiting the recruitment of these cells is beneficial in a wide range of diseases.

CCR5 is also a co-receptor for HIV-1 and other viruses, allowing these viruses to enter cells. Blocking the receptor with a CCR5 antagonist or inducing receptor internalisation with a CCR5 agonist protects cells from viral infection.

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 is **NHR^8**, **C_{1-6} alkyl** {optionally substituted with hydroxy or halo (for example fluoro) or phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **an N-linked 5- or 6-membered non-aromatic heterocyclic ring**, or **a non-aromatic, 5- or 6-membered mono-heteroatom heterocyclic ring, the heteroatom being oxygen or sulphur** {optionally substituted by C_{1-4} alkyl};

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is ethyl, allyl or cyclopropyl;

R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

k, m and n are, independently, 0, 1 or 2;

R^7 is C_{1-6} alkyl;

R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

or a pharmaceutically acceptable salt thereof or a solvate thereof; provided that when R^1 is optionally substituted alkyl, optionally substituted phenyl, optionally substituted heteroaryl [wherein heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or benzthiazolyl] or N-linked pyrrolidinyl, and R^2 and R^4 are both hydrogen then R^3 is not unsubstituted phenyl; and that when R^2 is hydrogen, R^4 is methyl and R^3 is unsubstituted phenyl then R^1 is not para-chlorophenyl.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers [for example tautomerism between oxo and hydroxy forms, such as on a heteroaryl ring]). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-

toluenesulphonate; or additionally, trifluoroacetate. In one aspect there is provided a compound of the invention which is in the form of a trifluoroacetate or hydrochloide salt.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Alkyl groups and moieties are straight or branched chain and are, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl or tert-butyl.

Halo includes fluoro, chloro, bromo and iodo; but is preferably fluoro or chloro.

Cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl.

N-Linked 5- or 6-membered non-aromatic heterocyclic rings may include a second heteroatom (such as another nitrogen atom or an oxygen or sulphur atom). Examples include piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl or thiomorpholinyl. The sulphur of thiomorpholinyl can be oxidised to an S-oxide or S-dioxide.

Non-aromatic, 5- or 6-membered mono-heteroatom heterocyclic ring, the heteroatom being oxygen or sulphur is, for example, tetrahydropyran or tetrahydrothiopyran. Such a group is optionally substituted by, for example, one or two C_{1-4} alkyl groups.

Heteroaryl is, unless specified otherwise, an aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulphur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heteroaryl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, thiazolyl, isothiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, [1,2,4]-triazolyl, pyridinyl, pyrimidinyl, indolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl, 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl (also known as benzo[1,2,3]thiadiazolyl), 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), quinolinyl, isoquinolinyl, a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a benzothiazinyl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Additionally heteroaryl is [1,2,3]-triazolyl, imidazo[2,1-b]thiazolyl, imidazo[1,2-c]pyrimidinyl or pyrrolo[2,3-c]pyridinyl. Heteroaryl is, for example, pyridinyl, pyrimidinyl or benzimidazolyl.

In one aspect the present invention provides a compound of formula (I) wherein: R^1 is NHR^8, C_{1-6} alkyl {optionally substituted with phenyl which is itself optionally substituted by

one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, or **an N-linked 5- or 6-membered non-aromatic heterocyclic ring**; R^2 is hydrogen or C_{1-6} alkyl; R^3 is phenyl or heteroaryl, either of which is optionally substituted in the ortho or meta position by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl; R^4 is hydrogen or C_{1-4} alkyl; R^5 is ethyl, allyl or cyclopropyl; R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; k, m and n are, independently, 0, 1 or 2; R^7 is C_{1-6} alkyl; R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}; or a pharmaceutically acceptable salt thereof or a solvate thereof; provided that when R^1 is optionally substituted alkyl, optionally substituted phenyl, optionally substituted heteroaryl [wherein heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or

benzthiazolyl] or N-linked pyrrolidinyl, and R^2 and R^4 are both hydrogen then R^3 is not unsubstituted phenyl; and that when R^2 is hydrogen, R^4 is methyl and R^3 is unsubstituted phenyl then R^1 is not para-chlorophenyl.

A compound of the invention wherein R^1 is **NHR^8**, **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by halo}, **phenyl** {optionally substituted by halo}, **heteroaryl** {optionally substituted by halo}, or **an N-linked 5- or 6-membered non-aromatic heterocyclic ring** (such as piperidinyl, pyrrolidinyl or morpholinyl); wherein R^8 is C_{1-6} alkyl {optionally substituted with phenyl which is itself optionally substituted by halo} or phenyl {optionally substituted by halo}. Heteroaryl is, for example, pyridinyl or benzimidazolyl.

In a further aspect R^1 is **NHR^8**, wherein R^8 is as defined above (for example R^8 is C_{3-7} cycloalkyl, such as cyclopentyl), or R^1 is N-linked piperidinyl, N-linked morpholinyl, tetrahydropyran, tetrahydrothiopyran or C_{1-4} fluoroalkyl having one to six fluorine atoms.

In another aspect the invention provides a compound of the invention wherein R^1 is **NHR^8**, wherein R^8 is as defined above. R^8 is, for example, C_{3-7} cycloalkyl such as cyclopentyl.

In yet another aspect R^1 is phenyl mono-substituted by fluoro, CF_3, $S(O)_2CH_3$ or $NHS(O)_2CH_3$; and R^3 is mono-fluoro phenyl.

In a further aspect the invention provides a compound of the invention wherein R^1 is N-linked piperidinyl, N-linked morpholinyl, tetrahydropyran, tetrahydrothiopyran or C_{1-4} fluoroalkyl having one to six fluorine atoms. In a still further aspect R^1 is N-linked piperidinyl or N-linked morpholinyl. In another aspect the invention provides a compound wherein R^1 is tetrahydropyran or tetrahydrothiopyran. In a still further aspect the invention provides a compound wherein R^1 is C_{1-4} fluoroalkyl having one to six, such as two to three, fluorine atoms. In another aspect R^1 is C_{2-4} trifluoroalkyl comprising a CF_3 group. Fluoroalkyl is, for example, CF_3CH_2 or $CF_3CH_2CH_2$.

In a further aspect the invention provides a compound wherein R^2 is hydrogen or C_{1-4} alkyl (such as methyl). R^2 is, for example, hydrogen.

In one aspect the phenyl or heteroaryl ring of R^3 is optionally substituted in the ortho or meta position relative to the position of attachment of that ring to the structure of formula (I). In another aspect the invention provides a compound of the invention wherein R^3 is phenyl {substituted in the ortho or meta position by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$

alkyl), nitro, cyano or CF_3}, heteroaryl {optionally substituted in the ortho or meta position by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3} or C_{5-7} cycloalkyl; n is 0, 1 or 2.

A compound of the invention wherein R^3 is phenyl {optionally substituted in the ortho or meta position (for example in the meta position) by halo (for example chloro or fluoro)}, thienyl or cyclohexyl.

In a still further aspect R^3 is phenyl optionally substituted (such as un-substituted or mono-substituted) by halo (such as chloro or fluoro; for example fluoro).

In another aspect of the invention R^3 is phenyl or 3-fluorophenyl.

In a further aspect the carbon to which R^3 is attached has the S absolute configuration. In a still further aspect the carbon to which R^3 is attached has the R absolute configuration.

A compound of the invention wherein R^4 is hydrogen or methyl. In a further aspect of the invention R^4 is methyl. In a still further aspect of the invention R^4 is hydrogen. In another aspect when R^4 is C_{1-4} alkyl (such as methyl) the carbon to which R^4 is attached has the R absolute configuration.

A compound of the invention wherein R^5 is ethyl.

In a still further aspect of the invention R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; and m is as defined above.

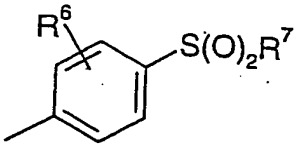
A compound of the invention wherein R^6 is halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; and m is as defined above.

A compound of the invention wherein R^6 is hydrogen.

A compound of the invention wherein R^6 is hydrogen, halo, hydroxy, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3.

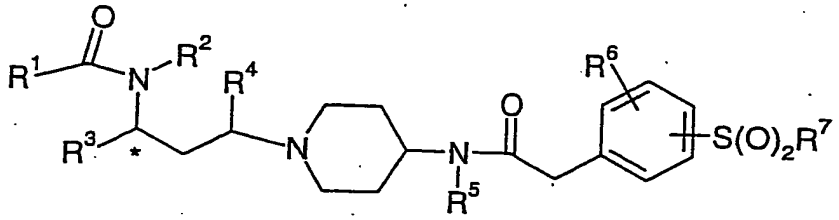
A compound of the invention wherein R^6 is halo, hydroxy, nitro, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3.

A compound of the invention wherein R^7 is C_{1-4} alkyl. For example R^7 is methyl. A compound of the invention wherein the $S(O)_2R^7$ group of formula (I) is para disposed to the remainder of the structure of formula (I), that is, it is as shown here:



The variables k, m and n are, for example, 0 or 2, for example they are all 2.

In another aspect the present invention provides a compound of formula (I):



(I)

wherein the compound has the S absolute configuration at chiral centre marked with an asterisk '*'; and

R^1 is **NHR^8, C_{1-6} alkyl** {optionally substituted with hydroxy or halo (for example fluoro) or phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **an N-linked 5- or 6-membered non-aromatic heterocyclic ring**, or **a non-aromatic, 5- or 6-membered mono-heteroatom heterocyclic ring, the heteroatom being oxygen or sulphur** {optionally substituted by C_{1-4} alkyl};

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is ethyl, allyl or cyclopropyl;

R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

k, m and n are, independently, 0, 1 or 2;

R^7 is C_{1-6} alkyl;

R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

or a pharmaceutically acceptable salt thereof or a solvate thereof.

In a still further aspect the present invention provides a compound of formula (I) wherein the compound has S absolute configuration at chiral centre marked with an asterisk '*'; and

R^1 is **NHR^8**, **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}; **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, or **an N-linked 5- or 6-membered non-aromatic heterocyclic ring;**

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is phenyl or heteroaryl, either of which is optionally substituted in the ortho or meta position by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is ethyl, allyl or cyclopropyl;

R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

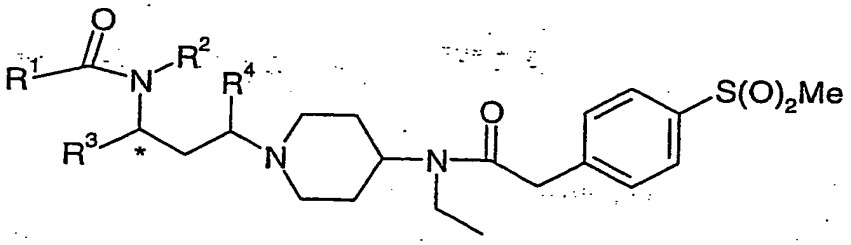
k, m and n are, independently, 0, 1 or 2;

R^7 is C_{1-6} alkyl;

R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}; **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

or a pharmaceutically acceptable salt thereof or a solvate thereof.

In a further aspect the present invention provides a compound of formula (Ia):



(Ia)

wherein R^1, R^2, R^3 and R^4 are as defined above; provided that when R^1 is optionally substituted alkyl, optionally substituted phenyl, optionally substituted heteroaryl [wherein heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or benzthiazolyl] or N-linked pyrrolidinyl,

and R^2 and R^4 are both hydrogen then R^3 is not unsubstituted phenyl; and that when R^2 is hydrogen, R^4 is methyl and R^3 is unsubstituted phenyl then R^1 is not para-chlorophenyl.

In a still further aspect the present invention provides a compound of formula (Ia) wherein the compounds of formula (Ia) have the S absolute configuration at chiral centre marked with an asterisk '*'; and wherein R^1, R^2, R^3 and R^4 are as defined above.

The following compounds illustrate the invention.

TABLE I

Table I comprises compounds of formula (Ia).

Compound No.	R^1	R^2	R^3	R^4	* Chirality	Adduct	LCMS (MH+)
1	6-Chloro-3-pyridinyl	H	Phenyl	H	S isomer		597
2	2-Chloro-4-pyridinyl	H	Phenyl	H	S isomer		597
3	Benzimidazol-5-yl	H	Phenyl	H	S isomer		602
4	1-Phenyl-1-methylethyl	H	Phenyl	H	S isomer		604
5	1-(4-Chlorophenyl)-1-methylethyl	H	Phenyl	H	S isomer		638
6	(1S)-1-Phenyl-2-methylprop-1-yl	H	Phenyl	H	S isomer		618
7	(1S)-1-Phenyleth-1-yl	H	Phenyl	H	S isomer		590
8	1-(4-Chlorophenyl)ethyl	H	Phenyl	H	S isomer		624
9	1-(4-Fluorophenyl)ethyl	H	Phenyl	H	S isomer		608
10	2,2-Dimethylpropyl	H	Phenyl	H	S isomer		556
11	Phenyl	H	Phenyl	H	S isomer		562
12	2-Fluorophenyl	H	Phenyl	H	S isomer		580
13	3,4-Difluorophenyl	H	Phenyl	H	S isomer		598
14	3-Fluorophenyl	H	Phenyl	H	S isomer		580
15	4-Chlorophenyl	H	Phenyl	H	R isomer		596
16	4-Chlorophenyl	H	Phenyl	H	S isomer		596

17	4-Fluorophenyl	H	Phenyl	H	S isomer		580
18	Piperidin-1-yl	H	Phenyl	H			569
19	Piperidin-1-yl	H	Phenyl	H	S isomer		569
20	Pyrrolidin-1-yl	H	Phenyl	H			555
21	Morpholin-4-yl	H	Phenyl	H			571
22	Morpholin-4-yl	H	Phenyl	H	S isomer		571
23	2-Phenylethylamino	H	Phenyl	H			605
24	1-Phenylethylamino	H	Phenyl	H			605
25	Phenylmethylamino	H	Phenyl	H			591
26	Ethylamino	H	Phenyl	H			529
27	iso-propylamino	H	Phenyl	H			543
28	Phenylamino	H	Phenyl	H			577
29	3-Chlorophenylamino	H	Phenyl	H			611
30	4-Chlorophenylamino	H	Phenyl	H			611
31	Propylamino	H	Phenyl	H			543
32	tert-butylamino	H	Phenyl	H			557
33	4-Chlorophenyl	H	Phenyl	Methyl	S isomer		610
34	Piperidin-1-yl	H	Thien-2-yl	H			575
35	Pyrrolidin-1-yl	H	Thien-2-yl	H			561
36	Morpholin-4-yl	H	Thien-2-yl	H			577

37	4-Chlorophenyl	H	Cyclohexyl	H			602
38	Phenyl	Methyl	Phenyl	H			576
39	4-Chlorophenyl	Methyl	Phenyl	H			610
40	Morpholin-4-yl	Methyl	Phenyl	H			585
41	Cyclohexylamino	H	Phenyl	H	S isomer		583
42	Cyclohexylamino	H	Thien-2-yl	H			589
43	Cyclohexylamino	H	Cyclohexyl	H			589
44	5-Methylisoxazol-4-yl	H	Phenyl	H	S isomer		567
45	Pyrazol-3-yl	H	Phenyl	H	S isomer		552
46	Thiazol-4-yl	H	Phenyl	H	S isomer		569
47	2-Methylimidazol-5-yl	H	Phenyl	H	S isomer		566
48	2-Methyloxazol-4-yl	H	Phenyl	H	S isomer		567
49	Isothiazol-5-yl	H	Phenyl	H	S isomer		569
50	[1,2,4]-Triazol-5-yl	H	Phenyl	H	S isomer		553
51	Thiazol-5-yl	H	Phenyl	H	S isomer		569
52	Furan-3-yl	H	Phenyl	H	S isomer		552
53	Pyrrol-2-yl	H	Phenyl	H	S isomer		551
54	Phenyl	H	Phenyl	Methyl	S isomer		
55	2-Fluorophenyl	H	Phenyl	Methyl	S isomer		
56	3,4-Difluorophenyl	H	Phenyl	Methyl	S isomer		

57	4-Fluorophenyl	H	Phenyl	Methyl	S isomer		
58	Piperidin-1-yl	H	Phenyl	Methyl	S isomer		
59	Pyrrolidin-1-yl	H	Phenyl	Methyl	S isomer		
60	Morpholin-4-yl	H	Phenyl	Methyl	S isomer		
61	Cyclopentylamino	H	Phenyl	H	S isomer		568
62	Isothiadiazol-3-yl	H	Phenyl	H	S isomer	hydrochloride	570
63	[1,2,3]-Thiadiazol-4-yl	H	Phenyl	H	S isomer	trifluoroacetate	570
64	Isoxazol-5-yl	H	Phenyl	H	S isomer	trifluoroacetate	553
65	4-Methyl-5-acetyl-pyrazol-3-yl	H	Phenyl	H	S isomer		608
66	3-Carbomethoxypyrazin-2-yl	H	Phenyl	H	S isomer		622
67	5-Methylfuran-2-yl	H	Phenyl	H	S isomer		566
68	6-Acetylaminopyridin-3-yl	H	Phenyl	H	S isomer	hydrochloride	620
69	5-Acetylthien-2-yl	H	Phenyl	H	S isomer		610
70	1-Methyl-4-chloropyrazol-5-yl	H	Phenyl	H	S isomer		601
71	4-Methylpyridin-2-yl	H	Phenyl	H	S isomer		577
72	5-Oxo-5,6-dihydroimidazo[1,2-c]pyrimidin-2-yl	H	Phenyl	H	S isomer		619
73	1H-Pyrrolo[2,3-c]pyridin-2-yl	H	Phenyl	H	S isomer		602
74	1,5-Dimethylpyrazol-3-yl	H	Phenyl	H	S isomer	trifluoroacetate	580
75	4,6-Dimethoxypyrimidin-5-yl	H	Phenyl	H	S isomer	trifluoroacetate	624

76	Imidazo[2,1-b]thiazol-6-yl	H	Phenyl	H	S isomer	trifluoroacetate	608
77	2-Methanesulfanylpyrimidin-4-yl	H	Phenyl	H	S isomer	trifluoroacetate	610
78	1,3-Dimethylpyrazol-5-yl	H	Phenyl	H	S isomer	trifluoroacetate	580
79	5-Methanesulfonylthien-2-yl	H	Phenyl	H	S isomer		646
80	3-Cyano-4-acetyl-5-methylpyrrol-2-yl	H	Phenyl	H	S isomer	trifluoroacetate	632
81	2,2-Dimethyltetrahydropyran-4-yl	H	Phenyl	H	S isomer		598
82	3,5-Difluorophenyl	H	Phenyl	H	S isomer	hydrochloride	598
83	Thiomorpholin-4-yl	H	Phenyl	H	S isomer		587
84	Difluoromethyl	H	Phenyl	H	S isomer	hydrochloride	536
85	4-Trifluoromethylpyridin-3-yl	H	Phenyl	H	S isomer	hydrochloride	631
86	2,2,2-Trifluoroethyl	H	Phenyl	H	S isomer	hydrochloride	568
87	4,4,4-Trifluorobut-2-yl	H	Phenyl	H	S isomer	hydrochloride	596
88	5-Trifluoromethylfuran-2-yl	H	Phenyl	H	S isomer	hydrochloride	620
89	6-Oxo-1,6-dihydropyridin-3-yl	H	Phenyl	H	S isomer		579
90	Imidazol-5-yl	H	Phenyl	H	S isomer		552
91	1,1-Dioxothiomorpholin-4-yl	H	Phenyl	H	S isomer		619
92	4-Isopropyl-[1,2,3]Triazol-5-yl	H	Phenyl	H	S isomer	hydrochloride	595
93	3-Cyanophenyl	H	Phenyl	H	S isomer	hydrochloride	587
94	4-Cyanophenyl	H	Phenyl	H	S isomer	hydrochloride	587
95	Tetrahydropyran-4-yl	H	Phenyl	Methyl	S isomer		584

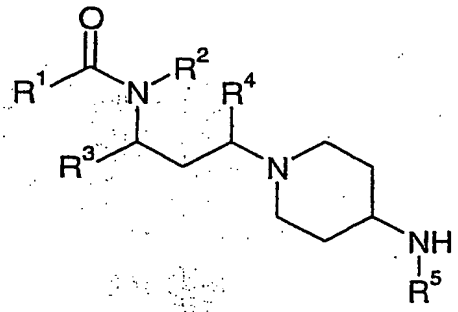
96	3,3,3-Trifluoropropyl	H	Phenyl	H	S isomer	hydrochloride	582
97	4-Acetylaminophenyl	H	Phenyl	H	S isomer		619
98	3-Methanesulfonylphenyl	H	Phenyl	H	S isomer		640
99	4-Methanesulfonylphenyl	H	Phenyl	H	S isomer		640
100	4-Methylaminosulfonylphenyl	H	Phenyl	H	S isomer		655
101	4-Methanesulfonylaminophenyl	H	Phenyl	H	S isomer		655
102	4-Trifluoromethylphenyl	H	Phenyl	H	S isomer		630
103	Phenyl	H	3-Fluorophenyl	H	S isomer		580
104	3-Fluorophenyl	H	3-Fluorophenyl	H	S isomer		598
105	Tetrahydropyran-4-yl	H	3-Fluorophenyl	H	S isomer		588
106	2,2-Dimethylpropyl	H	3-Fluorophenyl	H	S isomer		574
107	Piperidin-1-yl	H	3-Fluorophenyl	H	S isomer		587
108	2,2,2-Trifluoroethyl	H	3-Fluorophenyl	H	S isomer		586
109	Tetrahydrothiopyran-4-yl	H	Phenyl	H	S isomer		586
110	2-Methyl-2-hydroxypropyl	H	Phenyl	H	S isomer	hydrochloride	558
111	2,2,2-Trifluoroethyl	H	Phenyl	Methyl	S isomer		
112	3,3,3-Trifluoropropyl	H	Phenyl	Methyl	S isomer		
113	Isothiadiazol-3-yl	H	Phenyl	H	S isomer		
114	[1,2,3]-Thiadiazol-4-yl	H	Phenyl	H	S isomer		
115	Isoxazol-5-yl	H	Phenyl	H	S isomer		

116	6-Acetylaminopyridin-3-yl	H	Phenyl	H	S isomer		
117	1,5-Dimethylpyrazol-3-yl	H	Phenyl	H	S isomer		
118	4,6-Dimethoxypyrimidin-5-yl	H	Phenyl	H	S isomer		
119	Imidazo[2,1-b]thiazol-6-yl	H	Phenyl	H	S isomer		
120	2-Methanesulfanylpyrimidin-4-yl	H	Phenyl	H	S isomer		
121	1,3-Dimethylpyrazol-5-yl	H	Phenyl	H	S isomer		
122	3-Cyano-4-acetyl-5-methylpyrrol-2-yl	H	Phenyl	H	S isomer		
123	3,5-Difluorophenyl	H	Phenyl	H	S isomer		
124	Difluoromethyl	H	Phenyl	H	S isomer		
125	4-Trifluoromethylpyridin-3-yl	H	Phenyl	H	S isomer		
126	2,2,2-Trifluoroethyl	H	Phenyl	H	S isomer		
127	4,4,4-Trifluorobut-2-yl	H	Phenyl	H	S isomer		
128	5-Trifluoromethylfuran-2-yl	H	Phenyl	H	S isomer		
129	4-Isopropyl-[1,2,3]Triazol-5-yl	H	Phenyl	H	S isomer		
130	3-Cyanophenyl	H	Phenyl	H	S isomer		
131	4-Cyanophenyl	H	Phenyl	H	S isomer		
132	3,3,3-Trifluoropropyl	H	Phenyl	H	S isomer		
133	2-Methyl-2-hydroxypropyl	H	Phenyl	H	S isomer		

In another aspect the present invention provides each individual compound of Table I. In a further aspect the invention provides Compound No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 33, 44, 45, 46, 47, 48, 49, 50, 51, 52 or 53 of Table I, or a pharmaceutically acceptable salt thereof or a solvate thereof. In a still further aspect the invention provides Compound No. 54 to 133 of Table I, or a pharmaceutically acceptable salt thereof or a solvate thereof.

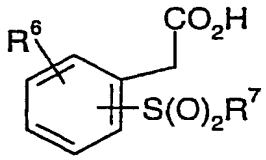
The compounds of the invention can be prepared as shown in the processes on pages marked Schemes 1 to 3 below. (In Schemes 1 to 3 Ac is acetyl; Boc is tert-butoxycarbonyl; Ph is phenyl; and, TFA is trifluoroacetic acid. Suitable coupling agents include PyBrOP (bromo-tris-pyrrolidino-phosphonium hexafluorophosphate) and HATU.)

A compound of the invention can be prepared by coupling a compound of formula (II):



(II)

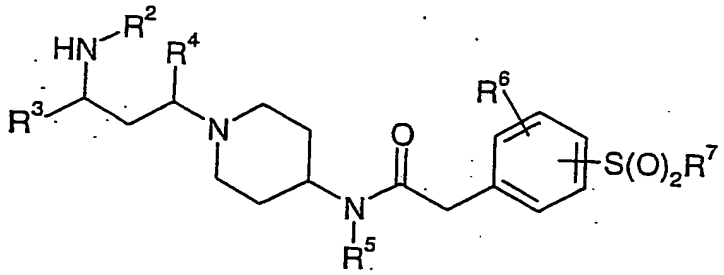
wherein R^1, R^2, R^3, R^4 and R^5 are as defined above, with a compound of formula (III):



(III)

wherein R^6 and R^7 are as defined above,in the presence of a suitable coupling agent (for example PyBrOP or HATU) in the presence of a suitable base (such as a tertiary amine, for example diisopropylethylamine) in a suitable solvent (for example *N*-methylpyrrolidinone or a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C).

Alternatively, a compound of the invention can be prepared by reacting a compound of formula (IV):



(IV)

wherein R^2, R^3, R^4 R^5, R^6 and R^7 are as defined above, with:

a) an acid of formula R^1CO_2H in the presence of a suitable coupling agent (for example PyBrOP or HATU) in the presence of a suitable base (such as a tertiary amine, for example diisopropylethylamine) in a suitable solvent (for example *N*-methylpyrrolidinone or a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C);

b) an acid chloride of formula $R^1C(O)Cl$ in the presence of a suitable base (such as a tertiary amine, for example triethylamine or diisopropylethylamine) in a suitable solvent (for example a chlorinated solvent, such as dichloromethane) at room temperature (for example 10-30°C);

c) an isocyanate of formula R^1NCO in the presence of a suitable base (such as a tertiary amine, for example triethylamine or diisopropylethylamine) in a suitable solvent (for example an ester such as ethyl acetate) at room temperature (for example 10-30°C); or,

d) a carbamoyl chloride in the presence of a suitable base (such as a tertiary amine, for example triethylamine or diisopropylethylamine);

wherein R^1 is as defined above.

The starting materials for all the processes and Schemes are either commercially available or can be prepared by literature methods, adapting literature methods or by following or adapting Methods herein described.

In a further aspect the invention provides processes for preparing the compounds of the invention. Many of the intermediates in the processes are novel and these are provided as further features of the invention.

The compounds of the invention have activity as pharmaceuticals, in particular as modulators (such as agonists, partial agonists, inverse agonists or antagonists) of chemokine receptor (especially CCR5) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated

diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

The compounds of the present invention are also of value in inhibiting the entry of viruses (such as human immunodeficiency virus (HIV)) into target calls and, therefore, are of value in the prevention of infection by viruses (such as HIV), the treatment of infection by viruses (such as HIV) and the prevention and/or treatment of acquired immune deficiency syndrome (AIDS).

According to a further feature of the invention there is provided a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in a method of treatment of a warm blooded animal (such as man) by therapy (including prophylaxis).

According to a further feature of the present invention there is provided a method for modulating chemokine receptor activity (especially CCR5 receptor activity) in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof or a solvate thereof.

The present invention also provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, as a medicament, especially a medicament for the treatment of transplant rejection, respiratory disease, psoriasis or arthritis (especially rheumatoid arthritis). [Respiratory disease is, for example, COPD, asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)} or rhinitis {acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}; and is particularly asthma or rhinitis].

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, for use as a medicament, especially a medicament for the treatment of rheumatoid arthritis.

In another aspect the present invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR5 receptor activity (especially rheumatoid arthritis)) in a warm blooded animal, such as man).

The invention further provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofoulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung or idiopathic interstitial pneumonia;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Phemphigus, bullous Phemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, Alopecia areata or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), Lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, leprosy (such as lepromatous leprosy), Peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a warm blooded animal, such as man.

The present invention further provides a method of treating a chemokine mediated disease state (especially a CCR5 mediated disease state) in a warm blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a warm blooded animal, such as man, in particular modulating chemokine receptor (for example CCR5 receptor) activity, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the invention, or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier. In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these

purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, aerosols, dry powder formulations, tablets, capsules, syrups, powders, granules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.

A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 0.01mgkg^{-1} to 100mgkg^{-1} of the compound, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1} of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of the invention, or a pharmaceutically acceptable salt thereof or a solvent thereof (hereafter Compound X), for therapeutic or prophylactic use in humans:

(a)

Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(c)

Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.0

(e)

Injection I	(50 mg/ml)
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl β-cyclodextrin may be used to aid formulation.

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) chromatography unless otherwise stated means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a "Bond Elut" column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI". Where an "Isolute™ SCX column" is referred to, this means a column containing benzenesulphonic acid (non-endcapped) obtained from International Sorbent Technology Ltd., 1st House, Duffryn Industial Estate, Ystrad Mynach, Hengoed, Mid Glamorgan, UK. Where "Argonaut™ PS-*tris*-amine scavenger resin" is referred to, this means a *tris*-(2-aminoethyl)amine polystyrene resin obtained from Argonaut Technologies Inc., 887 Industrial Road, Suite G, San Carlos, California, USA.

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields, when given, are for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio DMSO (CD_3SOCD_3) as the solvent unless otherwise stated; coupling constants (J) are given in Hz;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) solvent ratios are given in percentage by volume;

(ix) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (APCI) mode using a direct exposure probe; where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(x) LCMS characterisation was performed using a pair of Gilson 306 pumps with Gilson 233 XL sampler and Waters ZMD4000 mass spectrometer. The LC comprised water symmetry 4.6x50 column C18 with 5 micron particle size. The eluents were: A, water with 0.05% formic acid and B, acetonitrile with 0.05% formic acid. The eluent: gradient went from 95% A to 95% B in 6 minutes. Where indicated ionisation was effected by electrospray (ES); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$ and

(xi) the following abbreviations are used:

DMSO	dimethyl sulphoxide;
DMF	*N*-dimethylformamide;
DCM	dichloromethane;
THF	tetrahdydrofuran;
DIPEA	*N*,*N*-diisopropylethylamine;
NMP	*N*-methylpyrrolidinone;
HATU	O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
HBTU	O-(7-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate;
Boc	tert-butoxycarbonyl
MeOH	methanol;
EtOH	ethanol; and
EtOAc	ethyl acetate.

EXAMPLE 1

This Example illustrates the preparation of (*S*)-*N*-[1-(3-phenyl-3-benzoylamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 11 of Table I).

To a mixture of (*S*)-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Method A; 220mg, 0.42mmol) and DIPEA (0.75mL) in DCM (5mL) was added benzoic acid (100mg, 0.82mmol). To the resulting mixture was added HATU (300mg). The mixture was left at room temperature for 18 h, washed with 2M aqueous sodium hydroxide and water, then evaporated. Purification was achieved by BondElut chromatography eluting with a solvent mixture of ethyl acetate to 20% methanol in ethyl acetate to give the title compound (164mg); NMR (d^6-DMSO at 100°C): 1.1 (t, 3H), 1.5 (m, 2H), 1.75 (m, 2H), 2.0 (m, 4H), 2.35 (t, 2H), 2.9 (m, 2H), 3.13 (s, 3H), 3.25 (q, 2H), 3.82 (s, 2H), 3.85 (m, 1H), 5.15 (m, 1H), 7.2 - 7.5 (m, 10H), 7.85 (m, 4H), 8.52 (d, 1H); MS: 562.

The procedure described in Example 1 can be repeated using different carboxylic acids (such as 2-chloroisonicotinic acid, indole-5-carboxylic acid) in place of benzoic acid or different amines (such as (4'*S*)-*N*-[1-(4-phenyl-4-aminobut-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Method D)) in place of (*S*)-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride.

EXAMPLE 2

This Example illustrates the preparation of *(S)*-*N*-[1-(3-phenyl-3-[piperidin-1-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 19 of Table I).

To a mixture of (*S*)-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Method A; 200mg, 0.38mmol) and triethylamine (0.21mL) in DCM (10mL) was added 1-piperidinecarbonyl chloride (47µL, 0.38mmol) and the resulting mixture stirred at room temperature for 18h. The mixture was evaporated and the residue purified by eluting through a 20g BondElut cartridge giving the title compound (107mg, 50%); NMR ($CDCl_3$): 1.2 (t, 1H), 1.25 (m, 3H), 1.4 (t, 1H), 1.6 (m,

7H), 1.8 (m, 3H), 1.9 (m, 5H), 2.3 (m, 1H), 2.6 (m, 1H), 3.0 (s, 3H), 3.4 (m, 6H), 3.8 (m, 2H), 4.9 (m, 1H), 6.3 (m, 1H), 7.25 (m, 5H), 7,45 (d, 2H) 7.9 (d, 2H); MS: 569.

The procedure described in Example 2 can be repeated using different carbamoyl chlorides (such as 4-morpholinecarbonyl chloride and 1-pyrrolidinecarbonyl chloride) in place of 1-piperidinecarbonyl chloride, or different amines (such as *N*-[1-(3-[2-thienyl]-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method G)) in place of (*S*)-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride.

EXAMPLE 3

This Example illustrates the preparation of *N*-[1-(3-phenyl-3-[3-chlorophenylamino-carboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 29 of Table I).

Step 1: Preparation of *N*-[1-(3-phenyl-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of 3-phenyl-3-Boc-aminopropionaldehdye (4.6mg, 18.5mmol) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (6.0g, 18.5mmol) in DCM (100mL) and methanol (10mL) was added one drop of acetic acid and the resulting mixture was stirred at room temperature for 1h. Sodium triacetoxyborohydride (3.9g, 18.5mmol) was added and the mixture was stirred at room temperature for 18h. The reaction mixture was washed with saturated aqueous sodium bicarbonate solution (3 x 100mL), dried and evaporated. The residue was purified by silica gel chromatography (eluent: 1:1 ethyl acetate/isohexane then 15% methanol in ethyl acetate giving the sub-titled compound (11g).

Step 2: Preparation of *N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

N-[1-(3-phenyl-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (11g) was dissolved in trifluoroacetic acid (50mL) and the resulting mixture was stirred at room temperature for 2h. The mixture was evaporated and the residue treated with saturated aqueous sodium bicarbonate solution (150mL). The resulting mixture was extracted with diethyl ether (2 x 30mL). The aqueous phase was evaporated and the residue suspended in methanol (75mL). The resulting mixture was filtered and the residue

washed with methanol. The combined washings and filtrate were evaporated and the residue azeotroped with toluene to give the sub-titled compound (8.4g).

Step 3: Preparation of title compound

To a solution of *N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (230mg, 0.50mmol) and triethylamine (0.50mmol) in ethyl acetate (5mL) was added 3-chlorophenyl isocyanate (77mg, 0.50mmol) and the resulting mixture stirred at room temperature for 72h. The mixture was eluted through a silica gel column with ethyl acetate followed by 5% methanol in ethyl acetate to give the title compound (140mg, 46%); MS: 611.

The procedure described in Example 3 can be repeated using different isocyanates (such as phenyl isocyanate, ethyl isocyanate and 2-phenylethyl isocyanate) in place of 3-chlorophenyl isocyanate.

EXAMPLE 4

This Example illustrates the preparation *N*-[1-(3-cyclohexyl-3-[4-chlorobenzoylamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 37 of Table I).

To a solution of *N*-[1-(3-cyclohexyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method K, 250mg, 5.4mmol) and triethylamine (5.4mmol) in DCM (10mL) was added 4-chlorobenzoyl chloride (5.4mmol) and the resulting mixture was stirred at room temperature for 2h. Polymer supported isocyanate (200mg) and trisamine resin (200mg) were added and the mixture left standing at room temperature for 18h. The mixture was filtered, washed with saturated aqueous sodium hydrogen carbonate solution (2 x 20mL), dried and eluted through a 10g SCX cartridge with DCM then 10% methanol in DCM then methanol and finally 0.5M ammonia in methanol yielding the title compound as solid (169mg) after trituration with diethyl ether; NMR: 0.8-2 (m, 25H), 2.2 (m, 2H), 2.85 (m, 2H), 3.25 (s, 3H), 3.8 (m, 3H), 7.25 (m, 4H), 7.8 (m, 4H), 8.05 (d, 1H); MS: 602.

The procedure described in Example 4 can be repeated using different acid chlorides (such as benzoyl chloride) in place of 4-chlorobenzoyl chloride or different amines (such as *N*-[1-(3-phenyl-3-methylaminopropyl)-4-piperidinyl]-*N*-ethyl-4-

methanesulfonylphenylacetamide (Method P)) in place of *N*-[1-(3-cyclohexyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide.

EXAMPLE 5

This Example illustrates the preparation of (*S*)-*N*-{1-[3-(3,3,3-trifluoropropionylamino)-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonyl-phenyl)acetamide (Compound No. 108 of Table I).

To a stirred solution of 3,3,3-trifluoropropionic acid (32mg, 0.24mmol) in DCM (1mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.037mL, 0.23mmol) and the resulting mixture was stirred at room temperature for 1h. To this mixture was added a solution of (*S*)-*N*-{1-[3-amino-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonyl-phenyl)acetamide (Method R, 100mg, 0.21mmol) in DCM (1mL) and triethylamine (0.1mL, 0.65mmol) and the resulting mixture was stirred at room temperature for 18h. The mixture was diluted with DCM, washed with water and saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was purified by eluting through a BondElut cartridge (gradient elution DCM to 5% methanol in DCM) giving the title compound as a solid (52mg); NMR: 1.05 and 1.08 (t, 3H), 1.45 and 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 1.95 (m, 2H), 2.25 (t, 2H), 2.88 (m, 2H), 3.20 (s, 3H), 3.25 and 3.30 (q, 2H), 3.30 (s, 2H), 3.67 and 4.10 (m, 1H), 3.82 and 3.89 (s, 2H), 4.89 (m, 1H), 7.10 (m, 3H), 7.42 (m, 1H), 7.50 (d, 2H), 7.85 (d, 2H), 8.70 (dd, 1H); MS: 586 (MH+).

The procedure described in Example 5 can be repeated using different carboxylic acids (such as benzoic acid, 3-fluorobenzoic acid, tetrahydropyran-4-carboxylic acid, or 3,3-dimethylbutyric acid) in place of 3,3,3-trifluoropropionic acid.

EXAMPLE 6

This Example illustrates the preparation of (*S*)-*N*-[1-(3-phenyl-3-[1,1-dioxothiomorpholin-4-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 91 of Table I).

To a solution of (*S*)-*N*-[1-(3-phenyl-3-[thiomorpholin-4-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Example 7, 110mg, 0.188mmol) in 1:1 DMF/water (20mL) was added sodium tungstate (15mg) followed by 30% aqueous

hydrogen peroxide (0.5mL) dropwise. The resulting mixture was stirred at room temperature for 1h, diluted with water and extracted with DCM. The organic extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was dissolved in ethyl acetate and the solution washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by eluting through a 20g BondElut cartridge (gradient elution ethyl acetate to 40% methanol in ethyl acetate) giving the title compound as a solid (80mg); NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.52 (m, 2H), 1.80 (m, 2H), 1.90 (m, 2H), 1.98 (m, 3H), 2.40 (dd, 2H), 2.89 (m, 5H), 2.99 (m, 4H), 3.14 (s, 3H), 3.31 (q, 2H), 3.80 (s, 2H), 3.80 (m, 1H), 4.80 (dd, 1H), 6.85 (d, 1H), 7.18 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H); MS: 619 (MH+).

EXAMPLE 7

This Example illustrates the preparation of (*S*)-*N*-[1-(3-phenyl-3-[thiomorpholin-4-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 83 of Table I).

To a mixture of (*S*)-*N*-[1-(3-phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride (Method A; 1.3g, 2.4mmol) and DIPEA (2.6mL, 15mmol) in DCM (50mL) at 0°C under argon was added triphosgene (0.3g, 1.0mmol) and the resulting mixture stirred for 1h. 30mL of this mixture was added to a solution of thiomorpholine (0.15mL, 1.5mmol) in DCM (10mL) and the resulting mixture was stirred at room temperature for 1h. The mixture was evaporated and the residue partitioned between ethyl acetate and 2M aqueous sodium hydroxide. The organic phase was evaporated and the residue purified by eluting through a 20g BondElut cartridge (gradient elution ethyl acetate to 30% methanol in ethyl acetate) giving the title compound (105mg); NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.53 (m, 2H), 1.80 (m, 2H), 1.90 (m, 2H), 1.98 (m, 2H), 2.30 (dd, 2H), 2.50 (m, 4H), 2.89 (m, 2H), 3.14 (s, 3H), 3.31 (q, 2H), 3.66 (m, 4H), 3.80 (s, 2H), 3.80 (m, H), 4.80 (dd, 1H), 6.49 (d, 1H), 7.17 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H); MS: 587 (MH+).

There now follows NMR data for certain compounds of the invention.

(*S*)-*N*-[1-(3-phenyl-3-[2,2-dimethyltetrahydropyran-4-yl-carboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 81 of Table I).

NMR: 1.02 and 1.15 (t, 3H), 1.10 (s, 3H), 1.13 (s, 3H), 1.5 (m, 4H), 1.8 (m, 4H), 2.1 (m, 2H), 2.35 (m, 2H), 2.60 (m, 1H), 2.97 (m, 2H), 3.20 (s, 3H), 3.35 (m, 4H), 3.57 (m, 2H), 3.73 and 4.13 (m, 1H), 3.83 and 3.88 (s, 2H), 4.83 (m, 1H), 7.21 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 8.28 (br s, 1H).

(*S*)-*N*-[1-(3-phenyl-3-difluoroacetylaminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 84 of Table I).
NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.80 (m, 2H), 2.38 (m, 4H), 2.9-3.1 (m, 4H), 3.14 (s, 3H), 3.35 (q, 2H), 3.47 (m, 2H), 3.89 (s, 2H), 4.21 (m, 1H), 4.98 (dd, 1H), 6.20 (t, 1H), 7.30 (m, 1H), 7.35 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 9.12 (d, 1H), 11.0 (br s, 1H).

(*S*)-*N*-[1-(3-phenyl-3-[4-trifluoromethylpyridin-3-ylcarboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 85 of Table I).
NMR (d6-DMSO, 120°C): 1.15 (t, 3H), 1.80 (m, 2H), 2.38 (m, 4H), 3.0-3.2 (m, 4H), 3.14 (s, 3H), 3.33 (q, 2H), 3.50 (m, 2H), 3.88 (s, 2H), 4.21 (m, 1H), 5.13 (dd, 1H), 7.32 (m, 1H), 7.41 (m, 2H), 7.47 (m, 2H), 7.52 (d, 2H), 7.75 (d, 1H), 7.88 (d, 2H), 8.85 (s, 1H), 8.95 (m, 2H), 10.8 (br s, 1H).

(*S*)-*N*-[1-(3-phenyl-3-[3,3,3-trifluoropropionylamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 86 of Table I).
NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.75 (m, 2H), 2.28 (m, 2H), 2.37 (m, 2H), 2.9-3.1 (m, 4H), 3.14 (s, 3H), 3.33 (q, 2H), 3.35 (m, 2H), 3.48 (m, 2H), 3.83 (s, 2H), 4.20 (m, 1H), 4.95 (dd, 1H), 7.25 (m, 1H), 7.35 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 8.71 (d, 1H), 11.0 (br s, 1H).

(*S*)-*N*-[1-(3-phenyl-3-[3-cyanobenzoylamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 93 of Table I).
NMR: 1.10 and 1.25 (t, 3H), 1.80 (m, 2H), 2.31 (m, 4H), 3.20 (m, 4H), 3.27 (s, 3H), 3.40 (m, 2H), 3.50 (m, 2H), 3.90 and 3.97 (s, 2H), 4.18 and 4.39 (m, 1H), 5.20 (m, 1H), 7.31 (m, 1H), 7.42 (m, 2H), 7.55 (m, 3H), 7.78 (m, 1H), 7.90 (d, 2H), 8.10 (d, 1H), 8.28 (dd, 1H), 8.45 (d, 1H), 8.25 (m, 1H).

(3'*S*)-*N*-[1-(1-methyl-3-phenyl-3-[tetrahydropyran-4-yl-carboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 95 of Table I).

NMR: 0.90 (m, 3H), 1.05 and 1.19 (t, 3H), 1.5-2.1 (m, 12H), 2.10 (m, 4H), 2.40 (m, 2H), 2.60 (m, 3H), 2.70 (m, 1H), 3.22 (s, 3H), 3.35 (m, 4H), 3.65 and 3.98 (m, 1H), 3.83 and 3.88 (s, 2H), 4.93 (m, 1H), 7.21 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 8.25 (m, 1H).

(*S*)-*N*-[1-(3-phenyl-3-[4,4,4-trifluorobutyrylamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide hydrochloride (Compound No. 96 of Table I).
NMR (d6-DMSO, 120°C): 1.13 (t, 3H), 1.75 (m, 2H), 2.28 (m, 2H), 2.37 (m, 2H), 2.50 (m, 4H), 2.9-3.1 (m, 4H), 3.14 (s, 3H), 3.33 (q, 2H), 3.40 (m, 2H), 3.83 (s, 2H), 4.20 (m, 1H), 4.95 (dd, 1H), 7.25 (m, 1H), 7.35 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 8.40 (d, 1H), 11.0 (br s, 1H).

(*S*)-*N*-{1-[3-benzoylamino-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonyl-phenyl)acetamide (Compound No. 103 of Table I).
NMR: 1.02 and 1.15 (t, 3H), 1.45 and 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 1.95 (m, 2H), 2.30 (m, 2H), 2.88 (m, 2H), 3.20 (s, 3H), 3.25 and 3.30 (q, 2H), 3.67 and 4.07 (m, 1H), 3.82 and 3.89 (s, 2H), 5.10 (m, 1H), 7.02 (m, 1H), 7.20 (m, 2H), 7.45 (m, 1H), 7.50 (m, 5H), 7.85 (m, 4H), 8.90 (d, 1H).

(*S*)-*N*-{1-[3-(3-fluorobenzoylamino)-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonyl-phenyl)acetamide (Compound No. 104 of Table I).
NMR: 1.02 and 1.15 (t, 3H), 1.45 and 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 1.95 (m, 2H), 2.30 (m, 2H), 2.88 (m, 2H), 3.20 (s, 3H), 3.25 and 3.30 (q, 2H), 3.67 and 4.07 (m, 1H), 3.82 and 3.89 (s, 2H), 5.10 (m, 1H), 7.02 (m, 1H), 7.20 (m, 2H), 7.38 (m, 2H), 7.55 (m, 3H), 7.70 (m, 2H), 7.85 (d, 2H), 8.95 (d, 1H).

(*S*)-*N*-{1-[3-(3,3-dimethylbutyrylamino)-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonyl-phenyl)acetamide (Compound No. 106 of Table I).
NMR: 0.95 (s, 9H), 1.02 and 1.15 (t, 3H), 1.45 and 1.50 (m, 2H), 1.70 (m, 2H), 1.80 (m, 2H), 1.95 (m, 2H), 2.00 (ABq, 2H), 2.30 (m, 2H), 2.88 (m, 2H), 3.20 (s, 3H), 3.25 and 3.30 (q, 2H), 3.67 and 4.07 (m, 1H), 3.82 and 3.89 (s, 2H), 4.85 (m, 1H), 7.02 (m, 1H), 7.15 (m, 3H), 7.35 (m, 1H), 7.50 (d, 2H), 7.85 (d, 2H), 8.20 (dd, 1H).

(*S*)-*N*-[1-(3-phenyl-3-[tetrahydrothiopyran-4-yl-carboxyamino]propyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Compound No. 109 of Table I).

NMR: 1.05 and 1.19 (t, 3H), 1.5-2.1 (m, 12H), 2.30 (m, 2H), 2.65 (m, 4H), 2.90 (m, 1H), 3.22 (s, 3H), 3.35 (m, 4H), 3.73 and 4.13 (m, 1H), 3.83 and 3.88 (s, 2H), 4.83 (m, 1H), 7.21 (m, 1H), 7.30 (m, 4H), 7.50 (d, 2H), 7.85 (d, 2H), 8.25 (m, 1H).

Unless indicated otherwise all the final products were prepared using a method similar to that described for Example 1 using commercially available carboxylic acids with the exception of tetrahydrothiopyrancarboxylic acid (Compound No. 109 of Table 1) which was prepared according to: Helv. Chim. Acta. Vol. 80, **1997**, 1528-1545.

Starting materials are commercially available, have been described in the literature or can be prepared by adaptation of literature methods. Examples of literature methods include: P. Richter, Ch. Garbe and G. Wagner, *E. Ger. Pharmazie*, **1974**, *29(4)*, 256-262; C. Oniscu, D. Nicoara and G. Funieru, "4-(Ureidosulfonyl)phenylacetic acid and its ureide", *RO79-966646*, (Romanian document); and M. A. Zahran, M. M. Ali, Y. A. Mohammed and A. A. Shehata, *Int. J. Chem.*, **1993**, *4(3)*, 61.

Method A

(S)-N-[1-(3-Phenyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride

Step 1: Preparation of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride

To a solution of 1-phenylmethyl-4-piperidone (25.0g, 132 mmol) in THF (250mL) was added ethylamine hydrochloride (12.0g, 147mmol) and methanol (50mL) and the resulting mixture stirred at room temperature for 10min. Sodium triacetoxyborohydride (4 g, 189mmol) was added portionwise and the resulting mixture stirred at room temperature for 1h. 2M Sodium hydroxide solution (250mL) was added and the resulting mixture extracted with diethyl ether. The organic extracts were dried (K_2CO_3) and evaporated to give 1-phenylmethyl-4-ethylaminopiperidine as an oil. This was dissolved in ethanol (500mL) and concentrated hydrochloric acid (20mL) was added. The resulting crystals were collected, washed with diethyl ether and dried giving the sub-titled compound as a solid (38g); NMR ($CDCl_3$): 1.10 (t, 3H), 1.40 (m, 2H), 1.83 (m, 2H), 2.02 (m, 2H), 2.65 (q, 2H), 2.85 (m, 2H), 3.50 (s, 2H), 3.75 (m, 1H), 7.2 - 7.4 (m, 5H); MS: 219 (MH+).

Step 2: Preparation of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of 1-phenylmethyl-4-ethylaminopiperidine dihydrochloride (32.0g, 110mmol) in DCM (500mL) was added *N,N*-diisopropylethylamine (60mL) with stirring to ensure complete dissolution. 4-Methanesulfonylphenylacetic acid (25.0g, 117mmol), 4-dimethylaminopyridine (2.0g) and dicyclohexylcarbodiimide (25.0g, 121 mmol) were added and the resulting mixture was stirred at room temperature for 20 h. The precipitate was removed by filtration and the resulting solution was washed successively with 2N aqueous HCl, water and 1N aqueous NaOH, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: 10% MeOH/ethyl acetate) to afford the sub-titled compound (35 g, 76%); NMR: 1.00 and 1.14 (t, 3H), 1.45 and 1.70 (m, 2H), 1.95 (br m, 2H), 2.80 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.33 (q, 2H), 3.45 (s, 2H), 3.80 and 3.87 (s, 2H), 3.70 and 4.10 (m, 1H), 7.2 - 7.3 (m, 5H), 7.48 (m, 2H), 7.82 (m, 2H); MS: 415 (MH+).

Step 3: Preparation of *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of *N*-(1-phenylmethyl-4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenyl-acetamide (34g, 82mmol) in ethanol (600mL) was added ammonium formate (40g). The mixture was purged with argon and 30% Pd on carbon (4.2g) was added. The resulting mixture was stirred at reflux for 4 h, then allowed to cool and filtered through diatomaceous earth. The filtrate was evaporated to give a thick oil which solidified on standing to yield the sub-titled compound (24.9 g, 94%); NMR: 1.02 and 1.15 (t, 3H), 1.4 -1.6 (br m, 4H), 2.45 (m, 2H), 2.93 (br m, 2H), 3.18 (s, 3H), 3.20 and 3.32 (q, 2H), 3.72 and 4.18 (m, 1H), 3.80 and 3.87 (s, 2H), 7.50 (m, 2H), 7.85 (m, 2H); MS: 325 (MH+).

Step 4: Preparation of title compound

To a solution of (*S*)-3-phenyl-3-Boc-aminopropionaldehyde (Method B, 1.4g, 5.6mmol) in ethanol (100mL) and DCM (50mL) was added *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (2.0g, 6.2mmol), glacial acetic acid (0.6mL, 10mmol) and sodium triacetoxyborohydride (2.0g, 9.4mmol) and the resulting mixture was stirred at room temperature for 18 h. The mixture was partitioned between DCM and 2M aqueous sodium hydroxide (35mL), and the organic phase was washed with water, dried and concentrated. The residue was suspended in methanol (10mL) and concentrated hydrochloric acid (10mL) was added. The resulting mixture was stirred for 30 min. then evaporated. The residue was

azeotroped with ethanol and toluene and triturated with diethyl ether yielding the title compound as a solid (1.3g); NMR (d6 DMSO at 373K): 1.1 (t, 3H), 1.5 (m, 2H), 1.9 (m, 2H), 2.0 (m, 1H), 2.3 (m, 2H), 3.0 (m, 1H), 3.2 (m, 4H), 3.3 (q, 2H), 3.9 (s, 2H), 4.0 (m, 1H), 4.4 (m, 1H), 7.4 (m, 3H), 7.5 (m, 4H), 7.9 (m, 2H); MS: 458.

Method B

(*S*)-3-Phenyl-3-Boc-aminopropionaldehyde

To a solution of (*S*)-*N*-methyl-*N*-methoxy-3-phenyl-3-Boc-aminopropionamide (Method C, 5.52g, 17.9mmol) in toluene (180mL) at –20°C was added sodium bis(2-methoxyethoxy)aluminium hydride (65% solution in toluene, 35.8mmol) dropwise. The resulting mixture was stirred at –15°C for 1h. The mixture was washed with saturated aqueous sodium dihydrogen phosphate solution (250mL). The organic phase was dried (Na_2SO_4) and concentrated to give the title compound (5g); NMR: 1.4 (s, 9H), 2.8 (m, 2H), 5.1 (m, 1H), 7.3 (m, 5H), 8.6 (m, 1H), 9.6 (t, 1H).

Method C

(*S*)-*N*-Methyl-*N*-methoxy-3-phenyl-3-Boc-aminopropionamide

To a solution of (*S*)-3-phenyl-3-Boc-aminopropionic acid (available from PepTech Corp. of Cambridge, Massachusetts, USA; 4.97g, 18.7mmol) in DCM (100mL) was added DIPEA (14.8mL, 84.8mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.21g, 22.7mmol) followed by HATU (8.44g, 84.8mmol). The resulting mixture was stirred at room temperature for 18h, diluted with DCM, washed with 2M aqueous sodium hydroxide and water. The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica column chromatography (eluting with isohexane then 3:1 ethyl acetate to isohexane) giving the title compound as a colourless oil (5.58g, 97%); NMR ($CDCl_3$): 1.40 (s, 9H), 2.83 (dd, 1H), 3.01 (m, 1H), 3.08 (s, 3H), 3.52 (s, 3H), 5.10 (m, 1H), 7.28 (m, 5H); MS: 309.

Method D

(4'*S*)-*N*-[1-(4-Phenyl-4-aminobut-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide dihydrochloride

To (4'*S*)-*N*-[1-(4-phenyl-4-Bocaminobut-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method E, 194mg, 0.339mmol) was added 5M HCl in methanol (5mL) and the resulting mixture stirred at room temperature for 3h. The mixture

was evaporated and the residue azeotroped with toluene and triturated with diethyl ether to give the title compound as a white solid (178mg, 98%); MS: 472.

Method E

(4'*S*)-*N*-[1-(4-Phenyl-4-Bocaminobut-2-yl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

To a solution of (*S*)-4-phenyl-4-Boc-aminobutan-2-one (Method F, 1.25g, 4.75mmol) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (1.54g, 4.75mmol) in THF/1,2-dichloroethane (1:1, 45mL) was added titanium tetraisopropoxide (3.1mL, 10.45mmol) at room temperature. The resulting mixture was stirred for 15 min. before the addition of sodium triacetoxyborohydride (1.51g, 7.11mmol). The resulting mixture was stirred for 18h before addition of 2M aqueous sodium hydroxide (30mL). The mixture was diluted with DCM, filtered through Celite®, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by BondElut chromatography eluting with a mixture of 1% methanol and 0.05% ammonia in ethyl acetate giving the title compound as a white solid (1.04g); MS: 572.

Method F

(*S*)-4-Phenyl-4-Boc-aminobutan-2-one

To a solution of (*S*)-*N*-methyl-*N*-methoxy-3-phenyl-3-Boc-aminopropionamide (Method C, 2.02g, 6.56mmol) in THF (70mL) at –78°C was added methylmagnesium chloride (3M in THF, 21.1mmol) dropwise. The resulting mixture was stirred at –78°C for 30min. before warming to room temperature over 3h. The reacton mixture was added to a vigorously stirred mixture of diethyl ether, ice and 1M aqueous potassium dihydrogen phosphate. The aqueous phase was extracted twice with diethyl ether and the combined organic phases washed with sodium hydrogen carbonate solution (sat. aq.) and brine, dried (Na_2SO_4) and concentrated giving the title compound as a white solid (1.27g, 74%); NMR ($CDCl_3$): 1.41 (s, 9H), 2.09 (s, 3H), 2.91 (dd, 1H), 3.03 (m, 1H), 5.08 (m, 1H), 5.37 (br s, 1H), 7.28 (m, 5H); MS: 264.

Method G

N-[1-(3-[2-Thienyl]-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

N-[1-(3-[2-Thienyl]-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method H, 0.90g, 1.6mmol) was dissolved in trifluoroacetic acid (10mL) and the resulting mixture stirred at room temperature for 4h before evaporation. The residue was dissolved in DCM (25mL) and washed with 2M aqueous sodium hydroxide (2 x 25mL), dried and evaporated giving the title compound (470mg, 63%); NMR: 1.0 (m, 3H), 1.4-2 (m, 7H), 2.3 (m, 2H), 2.9 (m, 2H), 3.2 (s, 3H+H_2O), 3.3 (m, 2H), 3.9 (m, 2H), 4.1 (m, 1H), 6.9 (m, 2H), 7.3 (m, 1H), 7.5 (m, 2H), 7.8 (m, 2H).

Method H

N-[1-(3-[2-Thienyl]-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

To a mixture of 3-(2-thienyl)-3-Boc-aminopropionaldehyde (Method I, 1.5g, 5.8mmol) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (1.9g, 5.8mmol) in DCM (20mL) and ethanol (5mL) was added one drop of acetic acid. The resulting mixture was stirred at room temperature for 20min. before the addition of sodium triacetoxyborohydride (1.23g, 5.83mmol). The resulting mixture was stirred at room temperature for 18h. Polymer supported isocyanate resin (1g) was added and the resulting mixture was stirred at room temperature for 2h, filtered and eluted through a 10g SCX cartridge with DCM then methanol then 0.5M ammonia in isopropanol/methanol giving the title compound (0.9g); NMR: 1.0-1.1 (m, 3H), 1.4 (s, 9H), 1.4-4 (m, 8H), 2.3 (m, 2H), 2.95 (2m, 2H), 3.3 (s, 3H), 3.9 (d, 2 H), 4.8 (m, 1H), 6.9 (m, 2H), 7.3 (d, 1H), 7.5 (m, 3H), 7.8 (m, 2H).

Method I

3-(2-Thienyl)-3-Boc-aminopropionaldehyde

To a solution of 3-(2-thienyl)-3-Boc-aminopropan-1-ol (Method J, 1.5g, 3.9mmol) in DCM (50mL) was added Dess-Martin periodinane (2.5g, 3.9mmol) and the resulting mixture was stirred at room temperature for 2h. The reaction mixture was washed with 2M aqueous sodium hydroxide (2 x 50mL), dried and evaporated to give the title compound (1.5g) which was used in the next reaction without characterisation.

Method J

3-(2-Thienyl)-3-Boc-aminopropan-1-ol

To a solution of 3-(2-thienyl)-3-Boc-aminopropionic acid (2.4g, 8.85mmol) in THF (25mL) was added borane.THF complex (5.9mL, 1.5M, 8.85mmol) dropwise. The resulting mixture was stirred at room temperature for 4h. The mixture was cooled to 0°C and 2M aqueous sodium hydroxide was added. The mixture was extracted with ethyl acetate (3 x 50mL) and the combined extracts dried ($MgSO_4$) and evaporated giving the title compound (1.5g) which was used in the next reaction without characterisation.

Method K

N-[1-(3-Cyclohexyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

N-[1-(3-Cyclohexyl-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide (Method L, 9.4g, 20mmol) was dissolved in trifluoroacetic acid (30mL) and the resulting mixture was stirred at room temperature for 2h. Evaporation gave the title compound (3.6g); NMR: 0.8-1.85 (m, 25H), 2.3 (m, 3H), 2.8 (m, 2H), 3.1 (s, 3H+H_2O), 3.8 (d, 2H), 7.4 (d, 2H), 7.75 (m, 2H).

Method L

N-[1-(3-Cyclohexyl-3-Boc-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

To a mixture of 3-cyclohexyl-3-Boc-aminopropionaldehyde (Method M, 7g, 27mmol) and *N*-(4-piperidinyl)-*N*-ethyl-4-methanesulfonylphenylacetamide (9.6g, 27mmol) in DCM (200mL) and ethanol (20mL) was added acetic acid (0.5mL). The resulting mixture was stirred at room temperature for 30min. before the addition of sodium triacetoxyborohydride (5.8g, 27mmol). The resulting mixture was stirred at room temperature for 18h. The reaction mixture was washed with 2M aqueous sodium hydroxide (3 x 50mL), dried and evaporated. The residue was purified by silica gel chromatography (eluent: DCM then ethyl acetate then 10% methanol in ethyl acetate) giving the title compound (9.4g); NMR: 0.8-1.1 (m, 5H), 1.18 (s, 9H), 1.2-2 (m, 11H), 2.2 (m, 2H), 2.8 (m, 2H), 3.3 (s, 3H), 3.8 (d, 2H), 6.5 (d, 1H), 7.5 (m, 2H), 7.8 (m, 2H).

Method M

3-Cyclohexyl-3-Boc-aminopropionaldehyde

To a solution of *N*-methyl-*N*-methoxy-3-cyclohexyl-3-Boc-aminopropionamide (Method N, 9.9g, 31mmol) in toluene (100mL) at 0°C was added sodium bis(2-methoxyethoxy)aluminium hydride (65% solution in toluene, 31mmol) dropwise. The resulting mixture was stirred at 0°C for 2h. 2M aqueous sodium hydroxide was added and the mixture warmed to room temperature and filtered. The filtrate was washed with 2M aqueous sodium hydroxide (2 x 20mL), dried and evaporated giving the title compound (7g) which was used in the next reaction without characterisation.

Method N

N-Methyl-*N*-methoxy-3-cyclohexyl-3-Boc-aminopropionamide

To a solution of 3-cyclohexyl-3-Boc-aminopropionic acid (Method O, 8.6g, 32mmol) and HBTU (12.3g, 32mmol) in DMF was added triethylamine (32mmol) and the resulting mixture was stirred at room temperature for 10min. *N,O*-Dimethylhydroxylamine hydrochloride (3.3g, 32mmol) was added and the resulting mixture was stirred at room temperature for 18h before being evaporated. The residue was dissolved in ethyl acetate and the solution washed with water (3 x 75mL), dried and evaporated giving the title compound (9.9g); NMR: 0.8-1.2 (m, 6H), 1.6 (m, 5H), 2.4 (m, 1H), 3 (s, 3H), 3.05 (m, 1H), 3.6 (s, 3H), 3.7 (m, 1H), 6.5 (d, 1H).

Method O

3-Cyclohexyl-3-Boc-aminopropionic acid

To a mixture of 3-cyclohexyl-3-aminopropionic acid (5g, 30mmol), THF (20mL) and 2M aqueous sodium hydroxide (30mL, 58mmol) was added di-tert-butyldicarbonate (9.3g, 43mmol) and the resulting mixture was stirred at room temperature for 8h. Water (50mL) was added and the mixture extracted with DCM (2 x 50mL). The aqueous phase was acidified to pH 2 and extracted with DCM (5 x 25mL). The combined organic extracts were dried and evaporated giving the title compound (8.6g); NMR: 0.8-1.8 (m, 11H), 2.1-2.4 (m, 2H), 3.6 (m, 1H), 6.6 (d, 1H), 11.95 (s, 1H).

Method P

N-[1-(3-Phenyl-3-methylaminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide

This was prepared from 3-phenyl-3-methylaminopropionic acid (Method Q) using a similar sequence of reactions to that used to prepare *N*-[1-(3-cyclohexyl-3-aminopropyl)-4-piperidinyl]-*N*-ethyl-4-methanesulfonylphenylacetamide from 3-cyclohexyl-3-aminopropionic acid (Methods O-K).

Method Q

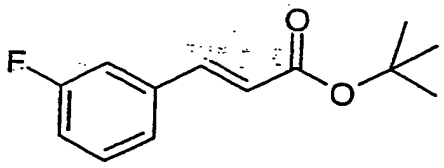
3-Phenyl-3-methylaminopropionic acid

Benzaldehyde (10.6g, 100mmol) was added to methylamine (50mL, 30% in ethanol) and the resulting mixture was stirred at room temperature for 2h then evaporated. The imine thus formed was dissolved in toluene (100mL) and malonic acid (10.4g, 100mmol) was added. The resulting mixture was heated to 90°C for 4h then allowed to cool to room temperature. The solid was collected by filtration to give the title compound (11g) which was used in the next reaction without characterisation.

Method R

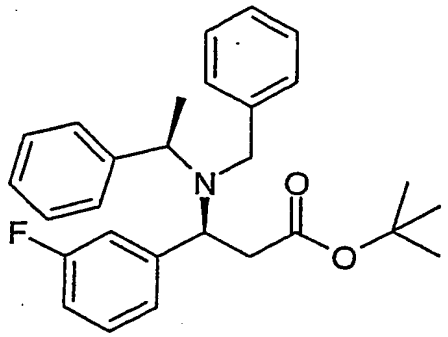
(*S*)-*N*-{1-[3-Amino-3-(3-fluorophenyl)propyl]piperidin-4-yl}-*N*-ethyl-2-(4-methanesulfonylphenyl)acetamide

Step 1: Preparation of *trans*-3-fluorocinnamic acid *tert*-butyl ester



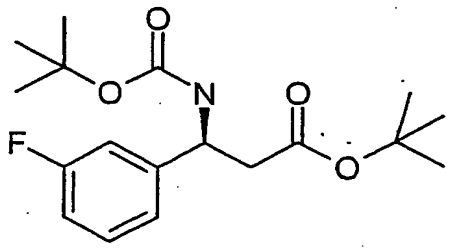
To a stirred solution of *trans*-3-fluorocinnamic acid (4.34g, 26.1mmol) in toluene (40mL) at 110°C was added *N,N*-dimethylformamide di-*tert*-butyl acetal (25mL, 104mmol) dropwise over 30 min. The resulting mixture was stirred at reflux for a further 4h. The mixture was then cooled to room temperature and washed with water (50mL), saturated aqueous sodium hydrogen carbonate solution (2 x 100mL) and brine (100mL), dried ($MgSO_4$) and evaporated. The crude product was purified by Bond Elut (isohexane then 2% ethyl acetate in isohexane) to give the title compound as a liquid (3.7g, 64%).

Step 2: Preparation of (*S*)-3-[(*R*)-benzyl-(1-phenyl-ethyl)-amino]-3-(3-fluoro-phenyl)-propionic acid *tert*-butyl ester



To a stirred solution of (*R*)-(+)-*N*-benzyl-α-methylbenzylamine (4.0mL, 19mmol) in THF (20mL) at –78°C was added n-butyl lithium (1.6M in hexanes, 12.5mL, 20mmol) and the resulting mixture was allowed to warm to room temperature over 10 min. before re-cooling to –78°C. A solution of *trans*-3-fluorocinnamic acid *tert*-butyl ester (3.74g, 16.8mmol) in THF (20mL) was added and the resulting mixture was stirred at –78°C for 2h then quenched by the addition of saturated aqueous ammonium chloride solution (25mL). After warming to room temperature the organic phase was washed with water (2 x 50mL) and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by Bond Elut (isohexane then 2% ethyl acetate in isohexane) to give the title compound as a gum (5.85g, 80%); NMR (400MHz, $CDCl_3$): 1.23 (s, 9H), 1.27 (d, 3H), 2.48 (m, 2H), 3.67 (s, 2H), 3.97 (q, 1H), 4.40 (dd, 1H), 6.93 (ddd, 1H), 7.1-7.4 (m, 13H).

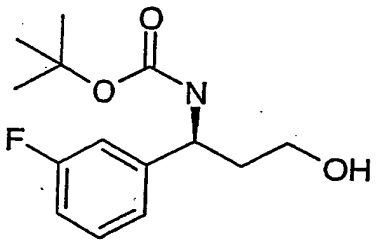
Step 3: Preparation of 3-*tert*-butoxycarbonylamino-3-(3-fluoro-phenyl)-propionic acid *tert*-butyl ester



A stirred mixture of (*S*)-3-[(*R*)-benzyl-(1-phenyl-ethyl)-amino]-3-(3-fluoro-phenyl)-propionic acid *tert*-butyl ester (5.39g, 12.4mmol), di-*tert*-butyl dicarbonate (2.98g, 13.7mmol) and 20% palladium hydroxide on carbon (0.59g) in ethanol (100mL) was hydrogenated at 5 Bar at room temperature for 24h. The catalyst was removed by filtration through a pad of

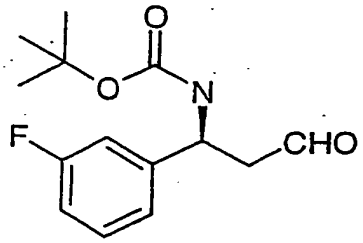
Celite® washing through with ethanol. The filtrate was evaporated to give an oil which was partitioned between ethyl acetate and saturated aqueous sodium hydrogen carbonate solution. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by Bond Elut (eluting with isohexane then 5% ethyl acetate in isohexane) to give the title compound as an oil (3.63g, 86%); NMR: 1.33 (s, 18H), 2.63 (m, 2H), 4.90 (m, 1H), 7.06 (ddd, 1H), 7.24 (m, 2H), 7.37 (dd, 1H), 7.50 (br d, 1H).

Step 4: Preparation of (*S*)-[1-(3-fluoro-phenyl)-3-hydroxy-propyl]-carbamic acid *tert*-butyl ester



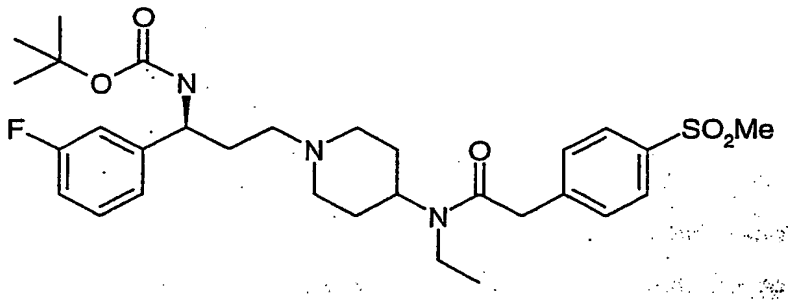
To a stirred, ice-cooled solution of 3-*tert*-butoxycarbonylamino-3-(3-fluoro-phenyl)-propionic acid *tert*-butyl ester (2.46g, 7.25mmol) in THF (35mL) was added lithium aluminium hydride (1M in THF, 7.50mL, 7.50mmol) dropwise over 20min. The resulting mixture was stirred with warming to room temperature for 2h. The reaction was quenched with water (0.275mL) then 15% aqueous sodium hydroxide (0.275mL) and more water (0.825mL) were added with stirring. The resultant precipitate was removed by filtration washing with THF, and the filtrate was dried ($MgSO_4$) and evaporated. The crude product was purified by Bond Elut (gradient elution, isohexane to 30% ethyl acetate in isohexane) to give the title compound as an oil (1.26g, 65%); NMR: 1.4 (s, 9H), 1.75 (m, 1H), 1.85 (m, 1H), 3.3 (m, 1H), 3.4 (m, 1H), 4.5 (dd, 1H), 4.65 (br m, 1H), 7.1 (m + br s, 3H), 7.35 (m, 2H).

Step 5: Preparation of (*S*)-[1-(3-fluoro-phenyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester



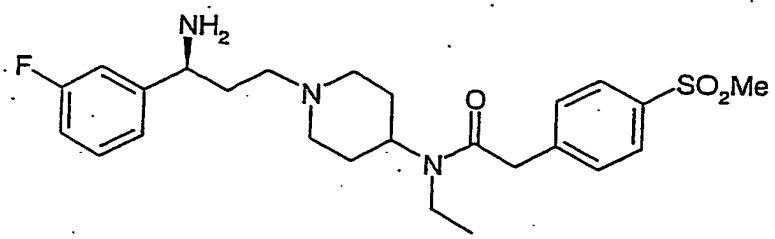
To a solution of (*S*)-[1-(3-fluoro-phenyl)-3-hydroxy-propyl]-carbamic acid *tert*-butyl ester (0.85g, 3.2mmol) in DCM (70mL) under argon was added Dess-Martin periodinane (1.48g, 3.5mmol) and the resulting mixture was stirred at room temperature for 2h before the addition of 2M aqueous sodium hydroxide (50mL). The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (quantitative); NMR: 1.4 (s, 9H), 2.8 (m, 2H), 5.1 (m, 1H), 7.05 (ddd, 1H), 7.15 (m, 2H), 7.35 (m, 1H), 7.5 (br d, 1H), 9.6 (s, 1H).

Step 6: Preparation of (*S*)-[3-(4-{ethyl-[2-(4-methanesulfonyl-phenyl)-acetyl]-amino}-piperidin-1-yl)-1-(3-fluoro-phenyl)-propyl]-carbamic acid *tert*-butyl ester



To a solution of (*S*)-[1-(3-fluoro-phenyl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester (0.85g, 3.12mmol) in DCM (70mL) and *N*-ethyl-2-(4-methanesulfonyl-phenyl)-*N*-piperidin-4-yl-acetamide (Method A, 1.19g, 3.67mmol) was added glacial acetic acid (one drop) and the resulting mixture was stirred at room temperature for 1h. Sodium triacetoxyborohydride (1.4g, 6.4mmol) was added and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was quenched with water and the organic phase was washed with sodium hydrogen carbonated solution (saturated aqueous) and water, dried ($MgSO_4$) and concentrated. The crude product was purified by Bond Elut (ethyl acetate then 8% methanol in ethyl acetate) to give the title compound as a solid (1.00g, 55%); NMR: 1.0 and 1.1 (t, 3H), 1.35 (s, 9H), 1.5 (m, 2H), 1.7 (m, 4H), 1.9 (m, 2H), 2.2 (t, 2H), 2.8 (m, 2H), 3.2 (s, 3H), 3.2 and 3.3 (q, 2H), 3.6 and 4.1 (m, 1H), 3.8 and 3.85 (s, 2H), 4.5 (m, 1H), 7.05 (m, 1H), 7.1 (m, 2H), 7.35 (dd, 1H), 7.5 (br d, 1H), 7.5 (d, 2H), 7.85 (d, 2H); LCMS: 576 (MH+).

Step 7: Preparation of title compound



To a solution of (*S*)-[3-(4-{ethyl-[2-(4-methanesulfonyl-phenyl)-acetyl]-amino}-piperidin-1-yl)-1-(3-fluoro-phenyl)-propyl]-carbamic acid *tert*-butyl ester (1.00g, 1.74mmol) in THF (30mL) and water (0.1mL) was added trifluoroacetic acid (5.0mL) and the resulting mixture was stirred at room temperature for 18h. The mixture was evaporated and the residue dissolved in DCM. This solution was washed with 2M aqueous sodium hydroxide, dried ($MgSO_4$) and evaporated to give the title compound (0.84g, quantitative); NMR: 1.05 and 1.09 (t, 3H), 1.45 and 1.50 (m, 2H), 1.75 (m, 4H), 1.95 (m, 2H), 2.25 (m, 2H), 2.88 (m, 2H), 3.20 (s, 3H), 3.25 and 3.30 (q, 2H), 3.67 and 4.08 (m, 1H), 3.82 and 3.89 (s, 2H), 7.00 (m, 1H), 7.15-7.40 (m, 3H), 7.50 (d, 2H), 7.85 (d, 2H), 8.70 (dd, 1H); MS: 476 (MH+).

EXAMPLE 8

The ability of compounds to inhibit the binding of RANTES was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated RANTES, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated RANTES bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated RANTES was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

EXAMPLE 9

The ability of compounds to inhibit the binding of MIP-1α was assessed by an *in vitro* radioligand binding assay. Membranes were prepared from Chinese hamster ovary cells which expressed the recombinant human CCR5 receptor. These membranes were incubated with 0.1nM iodinated MIP-1α, scintillation proximity beads and various concentrations of the compounds of the invention in 96-well plates. The amount of iodinated MIP-1α bound to the receptor was determined by scintillation counting. Competition curves were obtained for compounds and the concentration of compound which displaced 50% of bound iodinated

MIP-1α was calculated (IC_{50}). Preferred compounds of formula (I) have an IC_{50} of less than 50μM.

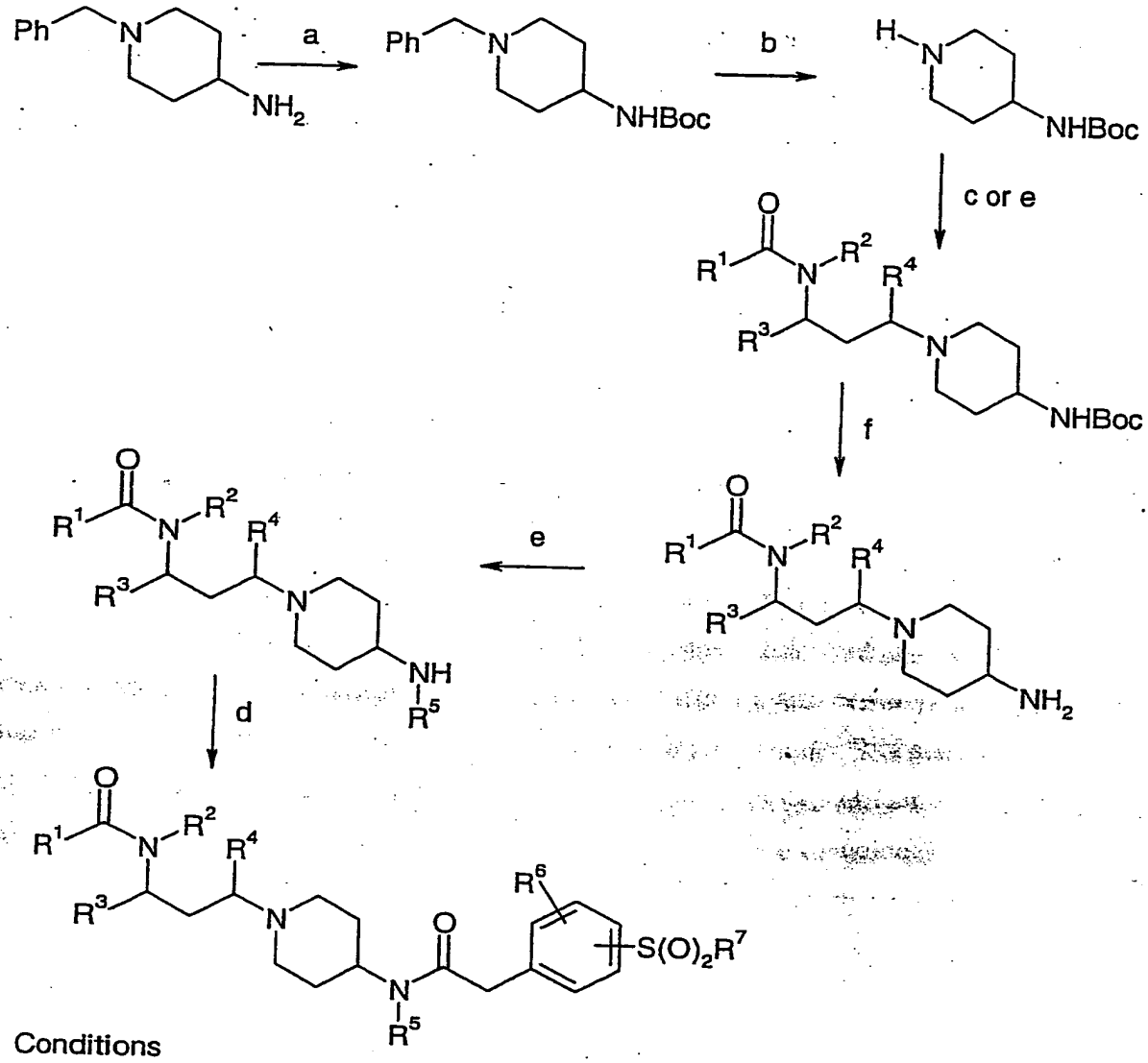
Results from this test for certain compounds of the invention are presented in Table II. In Table II the results are presented as Pic50 values. A Pic50 value is the negative log (to base 10) of the IC_{50} result, so an IC50 of 1μM (that is 1 x 10^{-6}M) gives a Pic50 of 6. If a compound was tested more than once then the data below is an average of the probative tests results.

Table II

Compound No.	Pic50
61	8.2
62	7.01
53	7.81
63	7.04
64	6.48
52	7.85
68	7.18
79	7.55
82	7.7
83	7.97
85	7.32
88	7.48
89	7.24
90	6.61
91	7.52
92	6.2
93	7.79
94	7.56
95	9.72

Compound No.	Pic50
97	7.57
98	7.84
99	7.39
100	7.63
101	8.33
102	8.02
103	9.36
104	9.35
105	8.54
106	9.25
107	9.03
109	9.27
81	7.7
84	7.45
86	8.7
87	7.79
96	8.63
108	8.02
110	7.34

SCHEME 1



Conditions

a) Boc_2O

b) Hydrogenation (H_2/Pd/C)

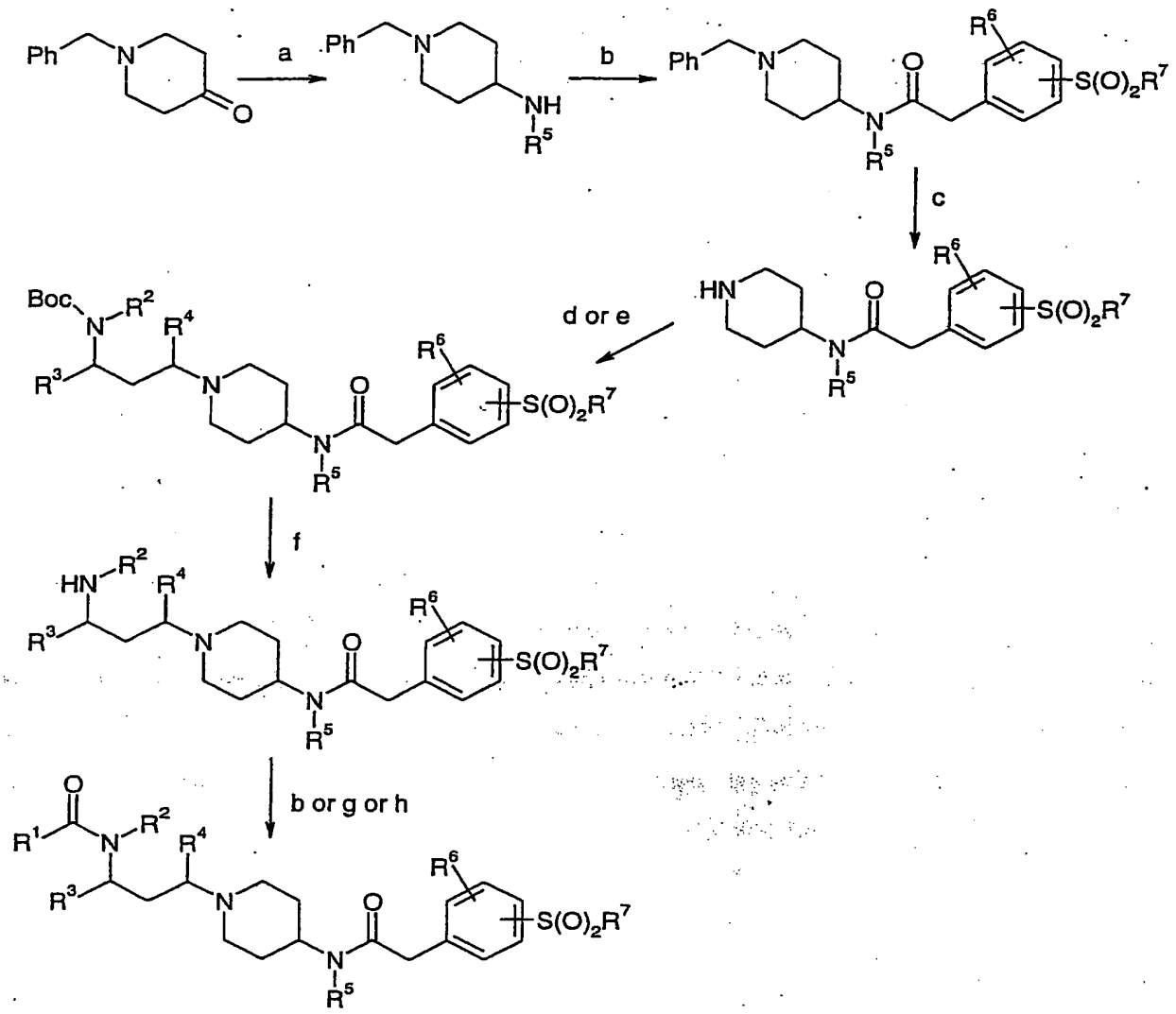
c) Alkyl halide, base

d) Amide formation (carboxylic acid and coupling reagent)

e) Reductive amination (aldehyde/ketone and $Na(AcO)_3BH$)

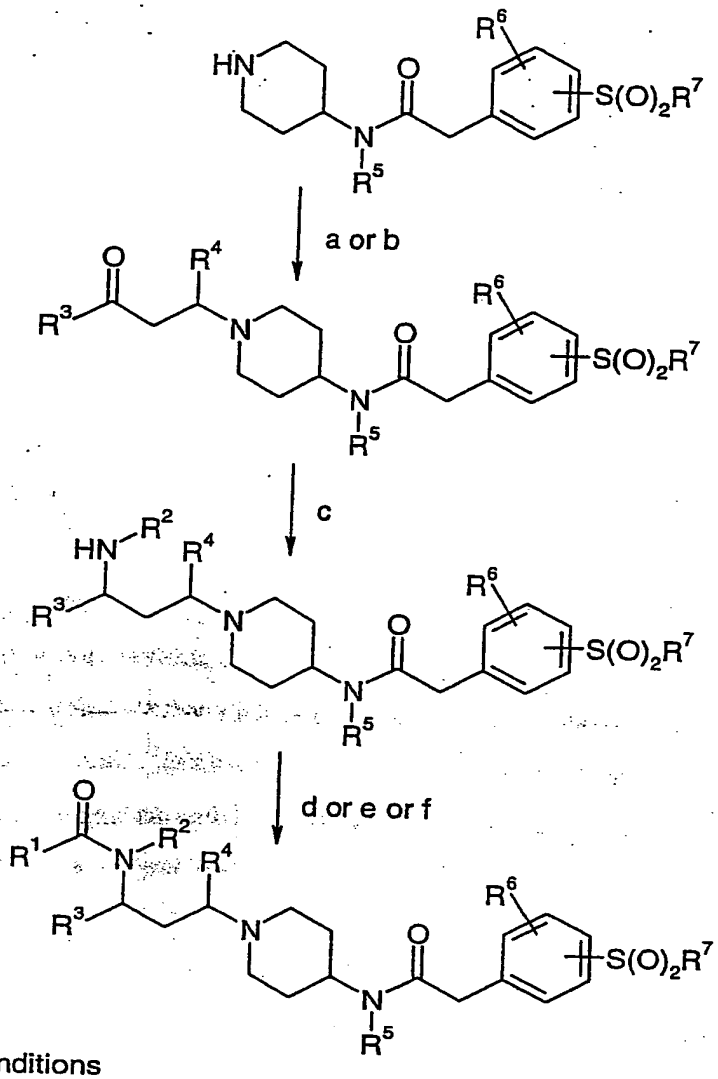
f) TFA or HCl/MeOH

SCHEME 2



Conditions
a) Reductive amination (amine and $Na(AcO)_3BH$)
b) Amide formation (carboxylic acid and coupling reagent or acid chloride, base)
c) Hydrogenation (H_2/Pd/C)
d) Alkyl halide, base
e) Reductive amination (aldehyde/ketone and $Na(AcO)_3BH$)
f) TFA or HCl/MeOH
g) Isocyanate, base
h) Carbamoyl chloride, base

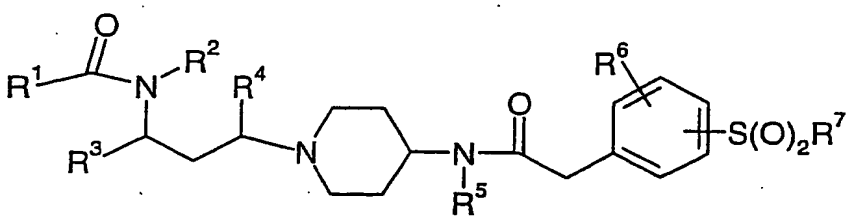
SCHEME 3



Conditions
a) Alkyl halide $R^3C(O)CH_2CHR^4L$, base
b) $R^3C(=O)CH_3$, CH_2O, Acetic acid (R^4=H)
c) Reductive amination
d) Amide formation (carboxylic acid and coupling reagent or acid chloride, base)
e) Isocyanate, base
f) Carbamoyl chloride, base

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is **NHR^8**, **C_{1-6} alkyl** {optionally substituted with hydroxy or halo (for example fluoro) or phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **an N-linked 5- or 6-membered non-aromatic heterocyclic ring, or a non-aromatic, 5- or 6-membered mono-heteroatom heterocyclic ring, the heteroatom being oxygen or sulphur** {optionally substituted by C_{1-4} alkyl};

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is ethyl, allyl or cyclopropyl;

R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$

alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

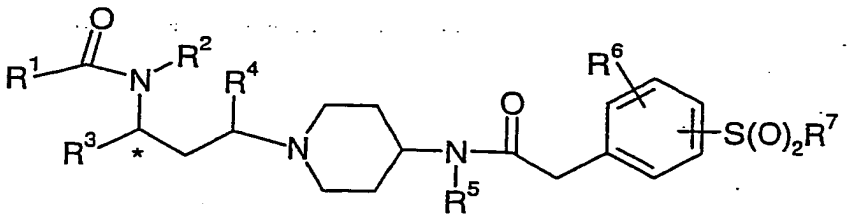
k, m and n are, independently, 0, 1 or 2;

R^7 is C_{1-6} alkyl;

R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};

or a pharmaceutically acceptable salt thereof or a solvate thereof; provided that when R^1 is optionally substituted alkyl, optionally substituted phenyl, optionally substituted heteroaryl [wherein heteroaryl is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, quinolinyl, isoquinolinyl, dihydroisoquinolinyl, indolyl, benzimidazolyl, benzo[b]furyl, benzo[b]thienyl, phthalazinyl, indanyl, oxadiazolyl or benzthiazolyl] or N-linked pyrrolidinyl, and R^2 and R^4 are both hydrogen then R^3 is not unsubstituted phenyl; and that when R^2 is hydrogen, R^4 is methyl and R^3 is unsubstituted phenyl then R^1 is not para-chlorophenyl.

2. A compound of formula (I):



(I)

wherein the compounds have the S absolute configuration at chiral center marked with an asterisk '*'; and

R^1 is NHR^8, **C_{1-6} alkyl** {optionally substituted with hydroxy or halo (for example fluoro) or phenyl which is itself optionally substituted by one or more of: halo,

hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **heteroaryl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **an N-linked 5- or 6-membered non-aromatic heterocyclic ring**, or **a non-aromatic, 5- or 6-membered mono-heteroatom heterocyclic ring, the heteroatom being oxygen or sulphur** {optionally substituted by C_{1-4} alkyl};

R^2 is hydrogen or C_{1-6} alkyl;

R^3 is phenyl or heteroaryl, either of which is optionally substituted by halo, C_{1-4} alkyl, C_{1-4} alkoxy, $S(O)_n(C_{1-4}$ alkyl), nitro, cyano or CF_3; or R^3 is C_{5-7} cycloalkyl;

R^4 is hydrogen or C_{1-4} alkyl;

R^5 is ethyl, allyl or cyclopropyl;

R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3;

k, m and n are, independently, 0, 1 or 2;

R^7 is C_{1-6} alkyl;

R^8 is **C_{1-6} alkyl** {optionally substituted with phenyl which is itself optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3}, **C_{3-7} cycloalkyl** or **phenyl** {optionally substituted by one or more of: halo, hydroxy, nitro, $S(O)_k(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy,

$C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3};
or a pharmaceutically acceptable salt thereof or a solvate thereof.

3. A compound as claimed in claim 1 or 2 wherein R^1 is phenyl mono-substituted by fluoro, CF_3, $S(O)_2CH_3$ or $NHS(O)_2CH_3$; and R^3 is mono-fluoro phenyl.

4. A compound as claimed in claim 1, 2 or 3 wherein R^1 is NHR^8, wherein R^8 is as claimed in claim 1 or 2, or R^1 is N-linked piperidinyl, N-linked morpholinyl, tetrahydropyran, tetrahydrothiopyran or C_{1-4} fluoroalkyl having one to six fluorine atoms.

5. A compound as claimed in claim 1, 2, 3 or 4 wherein R^2 is hydrogen.

6. A compound as claimed in claim 1, 2, 3, 4 or 5 wherein R^3 is phenyl optionally substituted by halo.

7. A compound as claimed in claim 1, 2, 3, 4, 5 or 6 wherein R^4 is hydrogen or methyl.

8. A compound as claimed in claim 1, 2, 3, 4, 5, 6 or 7 wherein R^5 is ethyl.

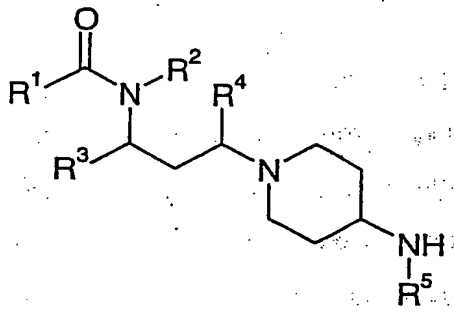
9. A compound as claimed in claim 1, 2, 3, 4, 5, 6, 7 or 8 wherein R^6 is hydrogen, halo, hydroxy, nitro, $S(O)_m(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl$)_2$, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl$)_2$, CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3; and m is 0, 1 or 2.

10. A compound as claimed in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein R^7 is C_{1-4} alkyl and wherein the $S(O)_2R^7$ group of formula (I) is para disposed to the remainder of the structure of formula (I).

11. Compound No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 33, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132 or 133 of Table I, or a pharmaceutically acceptable salt thereof or a solvate thereof.

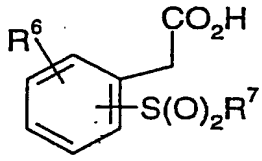
12. A process for the preparation of a compound as claimed in claim 1 or 2, the process comprising:

a) coupling a compound of formula (II):



(II)

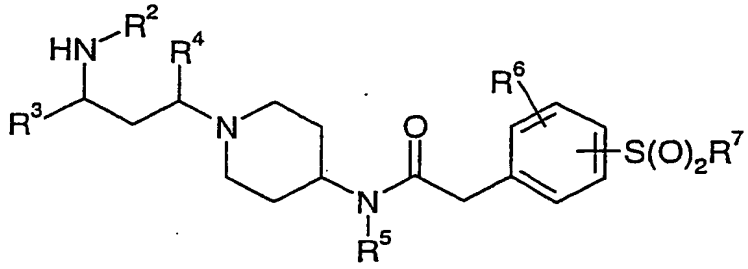
with a compound of formula (III):



(III)

in the presence of a suitable coupling agent, in the presence of a suitable base, in a suitable solvent; or,

b) reacting a compound of formula (IV):



(IV)

with:

i. an acid of formula R^1CO_2H in the presence of a suitable coupling agent in the presence of a suitable base, in a suitable solvent;

ii. an acid chloride of formula $R^1C(O)Cl$ in the presence of a suitable base, in a suitable solvent;

iii. an isocyanate of formula R^1NCO in the presence of a suitable base in a suitable solvent; or,

iv. a carbamoyl chloride in the presence of a suitable base.

13. A pharmaceutical composition which comprises a compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof or solvate thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof or solvate thereof, for use as a medicament.

15. A compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof or solvate thereof, in the manufacture of a medicament for use in therapy.

16. A method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1 or 2, or a pharmaceutically acceptable salt thereof or solvate thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02056

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/58, 401/12, 401/14, 405/12, 413/12, 409/12, 409/14, 417/12, A61K 31/4468, 31/4523, 31/5377, 31/541, A61P 1/00, 11/00, 17/00, 19/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA, EPO-INTERNAL, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02070479 A1 (ASTRAZENECA AB), 12 Sept 2002 (12.09.02), see especially compound 3 Table I and compound 3 Table Ii	1-16
P,X	WO 02076948 A1 (ASTRAZENECA AB), 3 October 2002 (03.10.02)	1-16
P,X	WO 02079156 A1 (ASTRAZENECA AB), 10 October 2002 (10.10.02)	1-16
P,X	WO 0187839 A1 (ASTRAZENECA AB), 22 November 2001 (22.11.01)	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2003	27-02-2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Viveca Norén/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/02056

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1013276 A1 (PFIZER INC.ET AL), 28 June 2000 (28.06.00), see especially examples 18 and 23 -- --------	1-16

INTERNATIONAL SEARCH REPORT

ional application No.
PCT/SE02/02056

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 16 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

30/12/02

International application No.
PCT/SE 02/02056

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02070479 A1	12/09/02	AU 2382102 A	01/07/02
		GB 0105077 D	00/00/00
		GB 0115579 D	00/00/00
		SE 0103797 D	00/00/00
WO 02076948 A1	03/10/02	GB 0107228 D	00/00/00
WO 02079156 A1	10/10/02	GB 0108046 D	00/00/00
WO 0187839 A1	22/11/01	AU 5898101 A	26/11/01
		GB 0011838 D	00/00/00
		NO 20025430 D	00/00/00
EP 1013276 A1	28/06/00	AP 200102186 D	00/00/00
		AP 200102187 D	00/00/00
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		AU 1675100 A	31/07/00
		BG 105709 A	28/02/02
		BG 105721 A	28/02/02
		BR 9905977 A	14/01/03
		BR 9916585 A	16/10/01
		BR 9917007 A	30/10/01
		CN 1331591 T	16/01/02
		CN 1331691 T	16/01/02
		EE 200100344 A	15/10/02
		EE 200100345 A	16/12/02
		EP 1140085 A	10/10/01
		EP 1140920 A	10/10/01
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		HR 20010478 A	30/06/02
		HU 0104795 A	29/04/02
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